Cardiac resynchronization induces major structural and functional reverse remodeling in patients with New York Heart Association class I/II heart failure.

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Cardiac Resynchronization Induces Major Structural and Functional Reverse Remodeling in Patients With New York Heart Association Class I/II Heart Failure

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Background—Cardiac resynchronization therapy (CRT) improves LV structure, function, and clinical outcomes in New York Heart Association class III/IV heart failure with prolonged QRS. It is not known whether patients with New York Heart Association class I/II systolic heart failure exhibit left ventricular (LV) reverse remodeling with CRT or whether reverse remodeling is modified by the cause of heart failure.

Methods and Results—Six hundred ten patients with New York Heart Association class I/II heart failure, QRS duration ≥120 ms, LV end-diastolic dimension ≥55 mm, and LV ejection fraction ≤40% were randomized to active therapy (CRT on; n=419) or control (CRT off; n=191) for 12 months. Doppler echocardiograms were recorded at baseline, before hospital discharge, and at 6 and 12 months. When CRT was turned on initially, immediate changes occurred in LV volumes and ejection fraction; however, these changes did not correlate with the long-term changes (12 months) in LV end-systolic (r=0.11, P=0.31) or end-diastolic (r=0.10, P=0.38) volume indexes or LV ejection fraction (r=0.07, P=0.72). LV end-diastolic and end-systolic volume indexes decreased in patients with CRT turned on (both $P<0.001$ compared with CRT off), whereas LV ejection fraction in CRT-on patients increased ($P<0.0001$ compared with CRT off) from baseline through 12 months. LV mass, mitral regurgitation, and LV diastolic function did not change in either group by 12 months; however, there was a 3-fold greater reduction in LV end-diastolic and end-systolic volume indexes and a 3-fold greater increase in LV ejection fraction in patients with nonischemic causes of heart failure.

Conclusions—CRT in patients with New York Heart Association I/II resulted in major structural and functional reverse remodeling at 1 year, with the greatest changes occurring in patients with a nonischemic cause of heart failure. CRT may interrupt the natural disease progression in these patients.

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Key Words: heart failure ■ cardiac resynchronization therapy ■ echocardiography ■ Doppler echocardiography ■ ventricular remodeling

Cardiac resynchronization is an established therapy for advanced heart failure (HF) because it prolongs survival, improves symptoms, and increases exercise capacity in patients with HF (New York Heart Association [NYHA] class III/IV), left ventricular ejection fraction (LVEF) ≤35%, and QRS duration ≥120 ms.[1–5] The salutary effects of cardiac resynchronization therapy (CRT) in patients with HF that is refractory to optimal medical treatment are associated with structural and functional left ventricular (LV) reverse remodeling.

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We hypothesized that CRT would result in LV reverse remodeling in NYHA class I and II HF patients that may delay disease progression to class III/IV. The specific aims of

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this prospective study were to determine whether patients with NYHA class I/II systolic HF exhibited LV reverse remodeling with CRT at 1 year, and if so, whether this reverse remodeling was modified by the cause of HF.

Methods

The REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study was a randomized, double-blind, controlled trial of CRT in patients with NYHA class I/II HF for at least 3 months before enrollment. All patients were in sinus rhythm with QRS duration ≥120 ms, LVEF ≤40%, and LV end-diastolic dimension ≥55 mm. Patient inclusion and exclusion criteria have been published previously.[6] All patients were receiving optimal medical HF therapy, which included stable doses of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker for a minimum of 1 month and a β-adrenergic receptor blocker for at least 3 months.[7,8] The ethics committee at each investigator site approved the protocol, and all patients gave written informed consent.

After baseline evaluation, patients underwent implantation of a CRT device with or without implantable cardioverter defibrillator capabilities and were then randomly assigned in a 2:1 model to active (CRT-ON) or control (CRT-OFF) conditions for 12 months. Two-dimensional, M-mode, and Doppler echocardiograms were recorded with an ECG at baseline, before hospital discharge (PHD), and at 6 and 12 months. Patients underwent 2 echocardiographic examinations at PHD and 2 echocardiographic examinations at 12 months. At PHD, the first echocardiogram was performed with CRT programmed off and the second with it programmed on after the device was optimized. The devices were then programmed according to the patients' randomization assignments. At 12-month follow-up, the first of the 2 echocardiograms was performed with CRT programmed on for patients randomized to CRT-ON, after which they underwent a 10-minute washout with CRT turned off before a second echocardiogram was performed with the CRT programmed off. The 10-minute washout period was to minimize any potential effect of CRT on LV loading conditions and therefore on LV volumes and LVEF. Likewise, at 12-month follow-up, patients randomized to CRT-OFF had the first echocardiogram performed with CRT programmed off and then the second with it programmed on.

The rationale for recording 2 echocardiograms at PHD with opposite programming was to determine whether immediate changes in LV volumes and LVEF predicted the changes in LV volume and LVEF at 12 months. The rationale for obtaining 2 echocardiograms at 12 months was to demonstrate that changes in LV volumes did not revert to baseline values when the CRT device was turned off but were sustained, reflecting true reverse remodeling at 1 year.

Patients assigned to CRT-ON were programmed to a mode that paced both ventricles and inhibited atrial pacing unless the intrinsic rate was ≤35 bpm. Patients assigned to CRT-OFF had the device programmed to inhibit atrial or ventricular pacing unless the intrinsic heart rate was ≤35 bpm. The time delay between atrial sensed activity and delivery of simultaneous biventricular pacing (AV delay) was optimized to maximize LV filling time without truncating left atrial contraction.[9]

Echocardiograms were analyzed in a core laboratory that was not informed of the randomization assignment. LV dimensions were recorded with 2D-directed M-mode echocardiography at the tips of the mitral valve leaflets. Echocardiograms were digitized to obtain LV volumes by Simpson's method of discs, as recommended by the American Society of Echocardiography,[10] from which LVEF was calculated. LV shape was computed at end diastole as the ratio of LV volume to the volume of a sphere with a diameter equal to LV cavity length in the apical 4-chamber view.[11] LV mass was calculated at end diastole as: [5/6×LV short-axis myocardial area×LV length×1.055] (1.055=the density of myocardium). The severity of mitral regurgitation (MR) was assessed from orthogonal apical echocardiographic images as the average area (measured by planimetry) of the Doppler color-encoded mitral regurgitant jet within the left atrium.

Transmitral Doppler signals were digitized to obtain the peak E-wave and peak A-wave velocities and deceleration time of the E wave. The myocardial performance index was calculated as the sum of isovolumic contraction time and isovolumic relaxation time divided by LV ejection time.[12] Interventricular mechanical delay (IVMD) was used as an indicator of interventricular dyssynchrony, defined as the time interval between the onset of antegrade blood flow in the right ventricular outflow tract and in the LV outflow tract. IVMD was estimated from the respective pulsed-wave Doppler velocity signals. QRS duration was used as an indicator of global LV dyssynchrony. Ischemic cardiomyopathy was defined as a history of myocardial infarction, coronary revascularization, and 2- or 3-vessel disease by coronary angiography, and nonischemic cardiomyopathy was defined as the absence of these criteria.[13]

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Statistical Methods

All end points were analyzed with the subjects included in their original randomized treatment group. All reported *P* values are nominal, and all tests were 2-sided. All data reported are from patients with analyzable echocardiograms. Where paired data were required, only data from patients with both data points were used. Echocardiographic parameters were measured as the absolute change between baseline (performed before CRT implantation) and 12 months (performed as randomized) for comparison between the 2 randomized groups. Unless otherwise indicated, echocardiographic data used in the analyses were collected with the patient's device programmed to the CRT mode to which the patient was randomized. Correlations between short- and long-term changes were tested with simple linear regression analysis. A 2-way ANOVA was used to assess the effect of randomization along with cause of HF on specific end points. *P* values that compared mean values of CRT-OFF versus CRT-ON were calculated with a 2-sample *t* test. *P* values that compared immediate changes were calculated with a paired *t* test. Baseline comparisons between percentages of CRT-OFF and CRT-ON patients were made with the Fisher exact test.

Results

A total of 684 patients were enrolled in the study, and a CRT device was successfully implanted in 621 patients. Eleven patients were not randomized for the following reasons: Inclusion criteria not met, complete heart block, atrial arrhythmias, LV lead dislodgment, loss of capture, death, HF status (n=2), and use of a surgical epicardial LV lead (n=3). Thus, the study population consisted of 610 patients, of whom 419 were randomized to CRT-ON and 191 to CRT-OFF. Baseline demographics were similar in the 2 groups (Table 1), as described previously.[14] Ninety-seven percent of patients were taking either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker, and 95% of patients were taking a β-blocker, which indicates that medical treatment was optimized in both groups.

For the overall population, mean LVEF was 26.7±7.0%, and mean LV end-diastolic dimension was 67±9 mm. The mean QRS duration was 153±22 ms. A CRT ICD was implanted in 83% of patients, and a CRT device alone was implanted in 17%.

Although REVERSE did not meet its primary end point of HF clinical composite response,[15] the study included LV end-systolic volume index (LVESVi) as a prospectively powered secondary end point and prespecified analyses to assess changes in cardiac structure and function by echocardiography.

Table 1. Baseline Demographics

Parameter	CRT-OFF (n=191)	CRT-ON (n=419)	*P*
Age, y	61.8±11.6	62.9±10.6	0.26
Male	152 (80)	327 (78)	0.75
NYHA classification (class II)	159 (83)	344 (82)	0.82
Ischemic HF	97 (51)	236 (56)	0.22
Diabetic	46 (24)	91 (22)	0.53
ACE inhibitors or ARBs	186 (97)	404 (96)	0.63
β-Blockers	179 (94)	401 (96)	0.32
Diuretics	148 (77)	339 (81)	0.33
QRS width, ms	154±24	153±21	0.41
LVEF, %	26.4±7.1	26.8±7.0	0.50
LVESVi, mL/m^2	102±43	99±35	0.51
Heart rate, bpm	68.2±10.9	66.9±10.3	0.17
Supine systolic blood pressure, mm Hg	123±19	125±19	0.25

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Values are mean±SD or n (%).

P values are 2-sided and were calculated with Fisher exact test or the 2-sample *t* test.

Paired baseline and 12-month echocardiograms at end systole were available in 163 of 191 CRT-OFF and 340 of 419 CRT-ON patients. Reasons for missing data were as follows (in chronological order; only the first reason was counted): Echocardiography not performed at baseline (n=1 CRT-OFF, n=2 CRT-ON), a technically limited echocardiogram at baseline (n=11 CRT-OFF, n=31 CRT-ON), death before the 12-month follow-up (n=2 CRT-OFF, n=9 CRT-ON), echocardiography not performed at 12 months (n=1 CRT-OFF, n=8 CRT-ON), and a technically limited echocardiogram at 12 months (n=13 CRT-OFF, n=29 CRT-ON).

Reverse Remodeling

Both LV end-diastolic volume index (LVEDVi) and LVESVi decreased from baseline to 12 months in the CRT-ON group compared with the CRT-OFF group (Figure 1; Table 2). These changes in LV volumes in NYHA class I/II patients were of similar magnitude to those reported in NYHA class III/IV HF patients with CRT.[2,16,17] Importantly, LV volumes in the 2 groups in REVERSE diverged between PHD and 12 months. The changes in LV volumes over 12 months in the CRT-ON group compared with the CRT-OFF group were associated with improvement in LVEF ($P<0.0001$) and restoration of LV cavity shape toward normal at end diastole ($P<0.01$; Figure 1; Table 2). In spite of the significant changes in LV volumes, shape, and ejection fraction in the CRT-ON group, there was no accompanying change in mean LV mass or severity of MR from baseline to 12 months compared with the CRT-OFF group (Table 2).

To assess whether CRT permanently remodels the LV, the changes in LVESVi, LVEDVi, and LVEF from baseline (before CRT implantation) to 12 months with CRT programmed off and the change from PHD (when CRT was first turned on temporarily in the CRT-OFF arm) to 12 months with CRT turned on were analyzed (Table 3). In all comparisons, the CRT-ON group demonstrated a greater change ($P<0.0001$) than the CRT-OFF group.

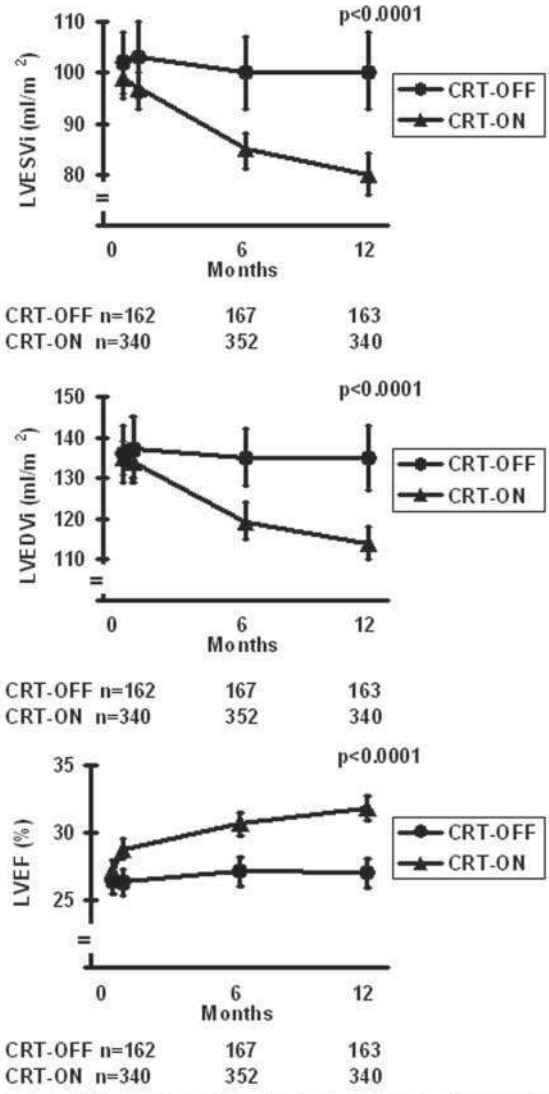

Figure 1. Time course of changes in echocardiographic estimates of LV volumes, dimensions, and ejection fraction in the CRT-ON and CRT-OFF groups. Baseline values were obtained before device implantation, after which CRT was either on at all subsequent time points or off at all subsequent time points.

Paired measurements of LV dimensions by 2D-directed M-mode echocardiography at baseline and 12 months in control and active-treatment groups were available in approximately 50% of patients. LV end-diastolic dimension and LV end-systolic dimension decreased from baseline through 12 months in the CRT-ON group ($P=0.005$ and $P=0.0004$ at 12 months between groups, respectively; Table 2) but did not change in the CRT-OFF group.

Echocardiographic measures of LV diastolic function did not change significantly between groups from baseline to 1 year Table 2). Improvement in diastolic function in responders to CRT is poorly understood but is believed to be due in part to "reverse molecular remodeling," typified by enhanced expression of calcium regulatory proteins. Also, in NYHA

Table 2. Echocardiographic Parameters Between CRT-ON and CRT-OFF Groups at Baseline and 12 Months

Parameter	Baseline	6 Months	12 Months
LVESVi, mL/m^2			
CRT-OFF	102±43 (179)	100±45 (175)	100±49 (172)
CRT-ON	99±35 (386)	85±36 (376)	80±35* (367)
LVEDVi, mL/m^2			
CRT-OFF	136±47 (179)	135±49 (175)	135±54 (172)
CRT-ON	135±41 (386)	119±41 (376)	114±40* (367)
LVEF, %			
CRT-OFF	26.4±6.7 (179)	27.1±7.3 (175)	27.0±7.1 (172)
CRT-ON	27.2±6.6 (386)	30.7±8.4 (376)	31.8±8.8* (367)
LVESD, cm			
CRT-OFF	5.79±1.09 (141)	5.91±1.10 (120)	5.80±1.27 (114)
CRT-ON	5.73±1.04 (271)	5.38±1.15 (278)	5.27±1.15* (252)
LVEDD, cm			
CRT-OFF	6.97±0.93 (141)	7.03±1.04 (120)	6.92±1.12 (115)
CRT-ON	6.92±0.94 (271)	6.61±1.04 (278)	6.51±1.05* (253)
MR, %			
CRT-OFF	16.1±13.0 (123)	15.1±13.6 (133)	15.9±12.7 (124)
CRT-ON	15.1±11.5 (273)	12.5±10.8 (254)	13.1±11.5 (240)
LV mass, g			
CRT-OFF	274±78 (126)	281±81 (121)	278±80 (111)
CRT-ON	269±76 (249)	258±69 (261)	255±70 (215)
IVMD, ms			
CRT-OFF	33.6±36.4 (166)	35.2±41.1 (166)	32.6±42.1 (155)
CRT-ON	33.9±40.1 (348)	22.0±36.8 (347)	22.2±35.3* (328)
MPI			
CRT-OFF	934±133 (163)	962±152 (163)	939±164 (154)
CRT-ON	965±134 (354)	961±146 (352)	963±147 (347)
LV cavity shape—diastole			
CRT-OFF	0.54±0.12 (179)	0.55±0.12 (175)	0.53±0.13 (172)
CRT-ON	0.53±0.12 (386)	0.50±0.12 (376)	0.48±0.12* (367)

LVESD indicates LV end-systolic diameter; LVEDD, LV end-diastolic diameter; and MPI, myocardial performance index.

Values in the table are mean±SD (n). Baseline values were recorded before implantation. Six-month and 12-month values were recorded with the patients in their randomized CRT mode.

*Between group P for change from baseline <0.01.

class I/II patients with systolic heart failure, diastolic dysfunction is not as advanced as it is in NYHA III/IV, so there is less substrate for improvement with CRT.

Early Transitory Changes Compared With Sustained Long-Term Changes

The first echocardiogram at PHD was performed with CRT turned off. The second echocardiogram was obtained after the CRT device was turned on and the device settings had been optimized. There were small but statistically significant early changes in LV volumes, LVEF, myocardial performance index, duration of LV filling, and the severity of MR when CRT was turned on at PHD (Table 4); however, these immediate changes in LV volumes and LVEF that occurred at PHD did not correlate with the corresponding changes in LVESVi ($r=0.11$, $P=0.31$), LVEDVi ($r=0.10$, $P=0.38$), or LVEF ($r=0.07$, $P=0.72$) that occurred between PHD and 12 months. Importantly, switching from CRT turned on to CRT off at 12 months did not result in any significant changes in LV volumes, MR, or myocardial performance index (Table 4).

Effect of HF Origin

CRT improved LV performance in both patients with ischemic HF and those with nonischemic HF, but the magnitude of improvements differed significantly between the 2 causes in favor of the nonischemic patients (Table 5). There was a 3-fold greater reduction in LVEDVi and LVESVi in CRT-ON patients with a nonischemic versus ischemic origin of HF from baseline to 12 months. There was also a more than 3-fold increase in LVEF in patients with a nonischemic versus an ischemic cause of HF at 12 months. In addition, regardless of the cutoff (5%, 15%, or 30% improvement), nonischemic CRT-ON patients improved more than any other group (Figure 2). When nonischemic and ischemic patients were compared, more than twice the percentage of CRT-ON patients had a >30% improvement compared with CRT-OFF patients. This included 52% of nonischemic HF CRT-ON patients and 20% of ischemic HF CRT-OFF patients with >30% improvement in LVESVi versus 15% and 7% of CRT-OFF patients with nonischemic and ischemic HF, respectively (Figure 2).

IVMD and QRS Duration in Relation to Reverse Remodeling

IVMD was divided into 3 groups (−40 ms or less; −40 to 40 ms; and >40 ms). This categorical variable, along with randomization, was used in a 2-way ANOVA. Randomization ($P<0.0001$), category of IVMD ($P<0.0001$), and their interaction ($P=0.0003$) were all significant factors, because there was a significant gradient in the reduction in LVESVi with an increase in IVMD (Figure 3). Similarly, QRS duration was divided into 3 groups (≤140 ms; >140 to ≤160 ms; and >160 ms). In another ANOVA model, randomization ($P<0.0001$), QRS width ($P<0.0001$), and their interaction ($P<0.0001$) were also significant predictors of change in LVESVi (Figure 3).

Discussion

CRT has proved efficacious in the treatment of NYHA III/IV class HF patients who are refractory to medical therapy by inducing LV reverse remodeling that improves survival.[18] Optimal medical therapy attenuates LV remodeling, with CRT providing additive reverse LV remodeling that is evident from the lack of change in mean LV volumes or mean LVEF in the control (CRT-OFF) group in REVERSE at 1 year. This additional LV reverse remodeling in the CRT-ON group occurred in spite of optimizing and stabilizing HF treatment before study participation. Ninety-seven percent of patients were taking angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and 95% were taking β-blockers in REVERSE. The lack of LV reverse remodeling in the control group in REVERSE is corroborated by CRT trials in advanced HF (NYHA class III/IV) in patients

Table 3. Comparison of Changes in Echocardiographic Parameters in the Same CRT Mode

Parameter	Baseline (CRT Not Yet Implanted)	12 Months CRT-OFF	Paired Difference	*P*	PHD CRT-ON	12 Months CRT-ON	Paired Difference	*P*
LVESVi, mL/m^2				<0.0001				<0.0001
CRT-OFF	102±43 (179)	100±49 (172)	−1.3±23.4 (163)		99±45 (158)	98±45 (164)	−0.2±21.2 (142)	
CRT-ON	99±35 (386)	81±36 (348)	−18.4±29.5 (324)		97±35 (359)	80±35 (367)	−15.6±27.3 (320)	
LVEDVi, mL/m^2				<0.0001				<0.0001
CRT-OFF	136±47 (179)	135±54 (172)	−1.4±28.0 (163)		135±51 (158)	132±50 (164)	−1.9±24.0 (142)	
CRT-ON	135±41 (386)	114±41 (348)	−20.5±33.4 (324)		134±39 (359)	114±40 (367)	−17.9±30.4 (320)	
LVEF, %				<0.0001				<0.0001
CRT-OFF	26.4±6.7 (179)	27.0±7.1 (172)	0.6±6.5 (163)		27.8±6.7 (158)	27.1±7.1 (164)	−0.8±6.5 (142)	
CRT-ON	27.2±6.6 (386)	30.8±8.7 (348)	3.8±9.3 (324)		28.7±7.1 (359)	31.8±8.8 (367)	3.0±9.2 (320)	

The columns on the left present between-group comparisons of changes in echocardiographic parameters from baseline (before CRT was implanted) to CRT turned off at 12 months after either 12 months of biventricular pacing (CRT-ON group) or no biventricular pacing (CRT-OFF group). The columns on the right present between-group comparisons of changes in echocardiographic parameters from PHD (when CRT was on) to CRT turned on at 12 months after either 12 months of biventricular pacing (CRT-ON group) or no biventricular pacing (CRT-OFF group).

P values compare paired differences between CRT-OFF and CRT-ON (2-sample *t* test).

randomized to CRT-OFF.[16] This is not to de-emphasize the important role of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and β-blockers, without which patients develop progressive LV dilatation, distortion of LV shape, and deteriorating function that culminates in worsening HF or arrhythmic death.[19,20]

Little is known about the potential use of CRT in patients with NYHA class I/II HF.[6] REVERSE demonstrated for the first time in a large, multicenter, randomized, double-blind, controlled study that CRT results in significant LV reverse remodeling, with changes in LV volumes and LVEF in NYHA class I/II HF patients comparable to those seen in NYHA class III/IV patients.[21] The favorable changes in LV volumes, shape, and LVEF with reverse remodeling occurred only in the CRT-ON group and not in the CRT-OFF group. Furthermore, LVEDVi and LVESVi in the CRT-ON group continued to diverge from the CRT-OFF group through 1 year, which indicates that LV reverse remodeling likely continues beyond 1 year, similar to findings in the CArdiac REsynchronization in Heart Failure (CARE-HF) trial.[17] Thus, CRT may remarkably delay or even stop the natural disease progression in patients with NYHA class I/II symptoms. There are important clinical implications of retarding the progression of NYHA class I/II to NYHA class III/IV HF by reverse remodeling with CRT.[15] These findings may be confirmed by ongoing trials in this same patient population.[22,23] Unlike the significant decrease in LV mass that occurred at 1 year in patients in NYHA class III/IV in MIRACLE (Multicenter InSync Randomized Clinical Evaluation), there was no change in LV mass in the NYHA class I/II HF patients in REVERSE at 12 months.[21] The decrease in LV volume without change in LV mass predictably lowered end-systolic wall stress, because there was no change in LV systolic pressure. Wall stress is a major determinant of LV architecture, myocardial composition, and function. Although the changes in biochemistry and electromechanical coupling with CRT have not been completely elucidated, downregulation of wall stress by CRT may be 1 mechanism that drives

Table 4. Immediate Changes in Echocardiographic Parameters When CRT Mode Is Changed

	All Patients: Parameters at PHD: Comparison of CRT-OFF vs CRT-ON Echocardiograms (Immediate Effects of Turning CRT-ON)			CRT-ON Patients Only: Parameters at 12 Months (Immediate Effects After 10-Minute "Washout" of Turning CRT-OFF)		
	n	CRT-OFF to CRT-ON (95% CI)	*P*	n	CRT-ON to CRT-OFF (95% CI)	*P*
LVESVi, mL/m^2	507	−2.93±10.62 (−3.86, −2.01)	<0.0001	343	0.75±10.45 (−0.35, 1.86)	0.18
LVEDVi, mL/m^2	507	−1.21±12.37 (−2.29, −0.13)	0.03	343	−0.25±12.53 (−1.58, 1.08)	0.71
LVEF, %	507	1.44±4.39 (1.05, 1.82)	<0.0001	343	−0.98±5.87 (−1.60, −0.35)	0.002
MR, %	432	−1.14±9.57 (−2.04, −0.23)	0.01	283	0.45±8.31 (−0.52, 1.42)	0.36
LV filling time/R to R interval, %	482	3.36±7.06 (2.73, 3.99)	<0.0001	332	−3.29±7.19 (−4.07, −2.52)	<0.0001
Myocardial performance index	464	8.34±66.92 (2.24, 14.45)	0.007	315	2.37±83.38 (−6.87, 11.62)	0.61
LV inflow, deceleration time, ms	428	9.68±55.27 (4.43, 14.94)	0.0003	317	−7.38±57.67 (−13.75, −1.00)	0.02

The columns on the left report immediate (mean) changes in echocardiographic parameters that occurred from PHD before CRT was turned on to after CRT was turned on at PHD. The columns on the right report mean changes in echocardiographic parameters that occurred only in CRT-ON patients at 12 months after a 10-minute washout of turning CRT off. Values are mean±SD.

Table 5. Relationship of HF Origin to Remodeling at 12 Months by CRT Group

	Nonischemic Cause of HF		Ischemic Cause of HF		ANOVA		
Parameter	CRT-OFF	CRT-ON	CRT-OFF	CRT-ON	Randomization	Origin/Cause	Interaction
LVESVi, mL/m^2	−6.6 (75)	−29.7 (149)	3.2 (88)	−9.6 (191)	<0.0001	<0.0001	0.04
LVEDVi, mL/m^2	−7.9 (75)	−30.5 (149)	4.2 (88)	−10.7 (191)	<0.0001	<0.0001	0.18
LVEF, %	1.12 (75)	7.61 (149)	0.24 (88)	2.24 (191)	<0.0001	<0.0001	0.004
MR, %	1.05 (59)	−1.90 (106)	0.47 (72)	−0.80 (166)	0.07	0.82	0.47
LV mass, g	−9.3 (47)	−24.1 (73)	−5.9 (48)	−11.5 (98)	0.12	0.22	0.48
IVMD, ms	2.3 (72)	−16.0 (114)	−2.0 (68)	−10.9 (162)	0.001	0.91	0.26
LV inflow, deceleration time, ms	4.1 (59)	24.6 (120)	−4.5 (79)	−8.24 (183)	0.34	0.02	0.17
Peak E/peak A	−0.12 (60)	−0.04 (127)	0.00 (82)	−0.05 (184)	0.86	0.39	0.36
LV cavity shape—diastole	−0.02 (75)	−0.07 (149)	0.00 (88)	−0.03 (191)	0.0003	0.008	0.33

The first 4 columns show the mean change from baseline to 12 months. The final 3 columns show the *P* values from an ANOVA with randomization, cause, and the interaction between randomization and cause of HF in the model. A significant interaction term indicates that the difference between CRT-OFF and CRT-ON is different between the ischemic and nonischemic populations. In addition, the change in LV cavity shape was greater in nonischemic patients.

the LV reverse-remodeling process. Wall stress also modulates the portfolio of stretch-activated matrix metalloproteinases that regulate the extracellular cellular collagen scaffold and facilitate changes in LV size.[24]

Another possible pathogenic mechanism for LV reverse remodeling was the reduction in dyssynchrony between baseline and 12 months. Evidence for decreased interventricular dyssynchrony was provided by the decrease in isovolumic contraction time and IVMD that occurred together with the prolonged, heart rate–adjusted LV filling time observed only in CRT-ON patients. Furthermore, there was a direct relationship between baseline IVMD and the extent of LV reverse remodeling. There was a similar relationship between baseline QRS duration and reduction in LVESVi, which indicates that the greater the global or interventricular dyssynchrony, the greater the propensity for LV reverse remodeling and the potential for clinical benefit.[5,14] Reduction in MR could not be implicated as a major cause of reverse LV remodeling in NYHA class I/II HF, because MR was present in only a minority of patients, was mild, and did not change in severity from baseline to 12 months.

The rationale for recording 2 echocardiograms (1 with CRT programmed on and a second with CRT programmed

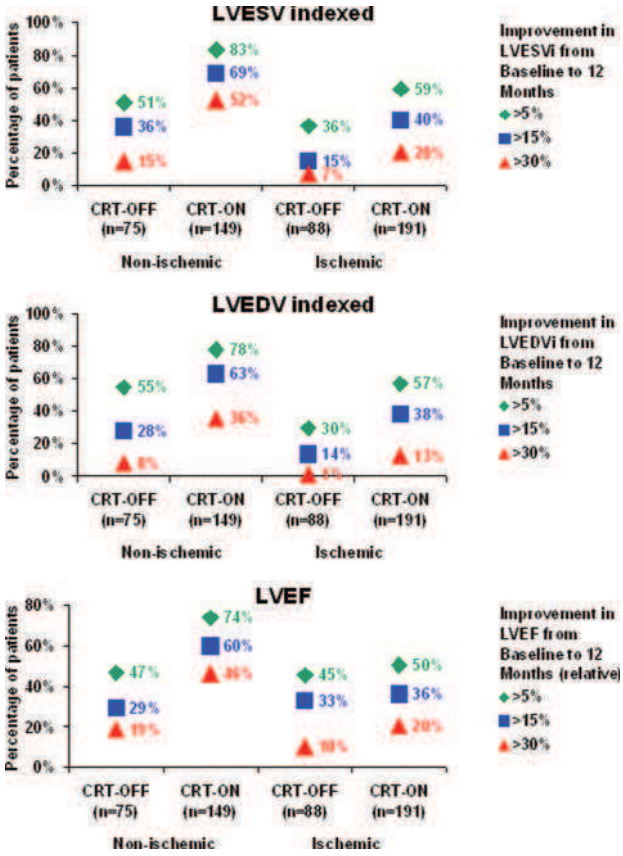

Figure 2. Effect of HF origin on LVESVi, LVEDVi, and LVEF; relative changes from baseline to 12 months. The percent of patients who improved with CRT and the magnitude of improvement at 3 arbitrarily chosen levels (5%, 15%, and 30%) are shown.

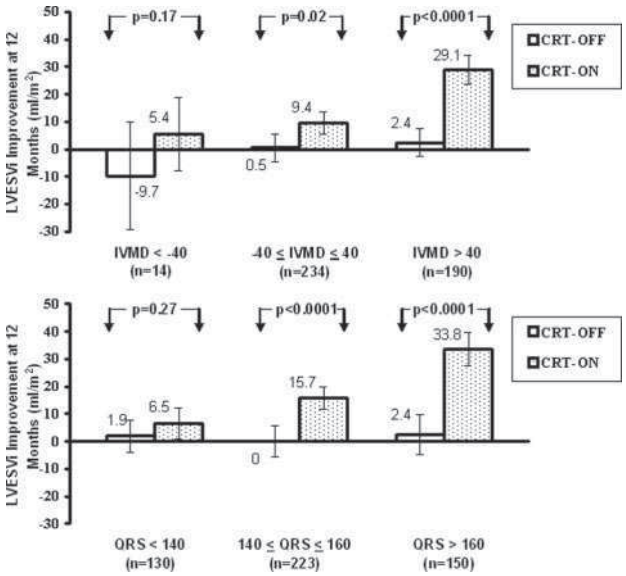

Figure 3. Relationship between IVMD and reduction in LVESVi (above) and between QRS duration and reduction in LVESVi (below) between CRT-ON and CRT-OFF groups. Mean±SD values are presented. *P* values are between groups (CRT-ON vs CRT-OFF) and are not adjusted for multiple comparisons. With Bonferroni correction for multiple comparisons, *P* values should be <0.05/3=0.0167 to be considered statistically significant.

off) at PHD and at 12 months was to discriminate between early transitory changes in LV volumes and LVEF and true sustained reverse LV remodeling. At PHD, there were significant early changes in LV dimensions, LV volumes, LVEF, and severity of MR (Table 4); however, these early changes in LV volumes and LVEF did not correlate with the changes in LVESVi at 12 months. In contrast, dramatic changes in LV volumes, LVEF, and MR were not observed at 12 months when CRT was turned off (Table 4), which indicates that by 1 year, the LV reverse remodeling with CRT had become sustained.

Approximately half of the patients in REVERSE (333/610, 54.5%) had HF due to ischemic heart disease, whereas 45.5% had HF of a nonischemic origin. Studies in patients with advanced HF have demonstrated differences in the reverse-remodeling response to CRT according to the cause of HF.[21] We demonstrated in REVERSE that CRT confers a 3-fold greater change in LV volumes and LVEF at 12 months in patients with nonischemic versus ischemic HF origin. These observations parallel findings in patients in NYHA class III/IV HF reported first in the MIRACLE trial[21] and likely represent a complement of irreversibly damaged ischemic myocytes that respond less to CRT.

Study Limitations

A potential limitation of the present study is found in the incomplete sets of echocardiographic linear measurements of LV end-diastolic and end-systolic dimensions, which amounted to approximately 50% of paired dimensions at baseline and at 12 months; however, the paired data for LV volumes were larger, and the significance and directional changes in LV dimensions and LV volumes between baseline and 12 months were concordant. Another potential limitation of the present study was the choice of a 10-minute "washout" period between the first of 2 echocardiograms performed at 12 months in patients randomized to CRT-ON. The first echocardiogram was obtained in these patients with the CRT device turned on and a second with it programmed off. The arbitrary 10-minute washout period was to demonstrate that changes in LV volumes did not revert to baseline values when CRT was turned off but instead were sustained, which reflects true reverse remodeling. Although there were no significant changes in LV volumes after a 10-minute washout period in the present study, such changes in volume may have occurred if we had chosen a washout period of 1 day or 1 week.

In conclusion, REVERSE shows for the first time that patients with NYHA class I/II HF respond to CRT similarly to those with NYHA class III/IV HF because of LV reverse remodeling. CRT resulted in favorable changes in LV architecture and function that occurred almost exclusively in CRT-ON patients, although both patient groups were given stable optimal medical therapy, often at target doses. The present findings that CRT provides incremental LV reverse remodeling compared with optimal medical therapy in NYHA class I/II HF may have important clinical implications in that CRT may delay or permanently interrupt the natural disease progression in these patients. This and ongoing studies may define an important therapeutic role for CRT in patients with NYHA class I/II HF, especially those with a nonischemic origin of HF.[21,24]

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CLINICAL PERSPECTIVE

Cardiac resynchronization therapy (CRT) has proved efficacious in New York Heart Association (NYHA) class III/IV heart failure (HF). This key echocardiographic study assessed the impact of CRT on structural and functional reverse remodeling in patients with NYHA class I/II HF. The REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial was a large, prospective, double-blind, controlled trial of CRT in patients with NYHA class I/II HF, a QRS ≥120 ms, left ventricular (LV) end-diastolic dimension ≥55 mm, and LV ejection fraction ≤40% who were randomly assigned to active therapy (CRT-on; n=419) or control (CRT-off; n=191). Doppler echocardiograms were recorded at baseline, before hospital discharge, and at 6 and 12 months. The present study showed that CRT in patients with NYHA class I/II HF who were already receiving optimal therapy with a β-blocker (95%), angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker (97%) resulted in LV reverse remodeling with favorable changes in LV volume, shape, and ejection fraction similar to those that occurred in patients in NYHA class III/IV; however, there were no accompanying changes in LV diastolic function, LV mass, or severity of mitral regurgitation. There was 3-fold greater LV reverse remodeling in patients with a nonischemic origin of HF than in those with an ischemic origin. Our findings have potentially important clinical implications in that CRT may delay or interrupt the natural disease progression of HF in these patients. This and ongoing studies may define an important therapeutic role for CRT in patients with NYHA class I/II, as well as class III/IV HF, especially those cases with a nonischemic cause.

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